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MINIREVIEW

One, Two, or Three Step: Measles Virus Receptor Dance

Michael B. A. Oldstone,*[,1] Dirk Homann,* Hanna Lewicki,* and Donald Stevenson†

Division of Virology, Department of Neuropharmacology, The Scripps Research Institute, and †Division of Allergy, Department of Medicine, Scripps Clinic Medical Group, 10550 North Torrey Pines Road, IMM-6, La Jolla, California 92037-1092

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Introduction. Measles virus (MV) is one of the most contagious viruses known to humans, primarily causing an acute disease (Katz, 1985; Griffin, 2001), with attack rates in virgin populations >90% (Katz, 1985; Griffin, 2001; Oldstone, 1998). After an incubation period of approximately 11 days, clinical manifestations characterized by fever, coryza, cough, conjunctivitis, exanthematous rash, photophobia, and headache occur. These clinical findings complemented by laboratory studies point to involvement of the nasal–respiratory mucosal tract, lymphoid organs, alimentary tract, and central nervous system (CNS) during this infection.

Observations in humans and nonhuman primates indicate that during the first 2 days of the incubation period, MV replicates in nasal, tracheal, bronchial, and pulmonary epithelial cells (Katz, 1985; Griffin, 2001; McChesney *et al.,* 1997; Sakaguchi *et al.,* 1986). Later virus can be isolated from nasal and throat washings. Virus is believed to be transmitted from the respiratory tract to local lymphoid tissues but, as suggested in the accompanying minireview by Yanagi *et al.* (2002), may possibly initially infect activated lymphoid cells, although there is as yet no direct evidence for this assumption. Nevertheless, MV was first isolated from buffy-coat lymphoid cells (Peebles, 1967) in the blood and is easily obtained from lymphoid cells during the course of infection.

Replication in lymphoid tissues *in vivo* gives rise to syncytia or reticuloendothelial giant cells (Warthin–Finkeldey cells). Dendritic cells (DC) resident in mucosal tissues play an important role in local immune surveillance against invading pathogens. DC in the respiratory tract are located within the upper layers of epithelial cells and extend their dendritic processes toward the luminal side of tissues; these DC are important for the uptake of virus penetrating through surface epithelial and for transporting that material for presentation to T cells in draining lymph nodes where specific immune responses are initiated (Schon-Hegrad *et al.,* 1991). DC from humans can be grown *in vitro* from a number of sources (i.e., cord blood, skin), and Langerhans cells, mature circulating blood DC, and immature DC from blood monocytes have been reported as permissive to and productively infected by MV Edmonston, MV Halle, or wt MV (Bhardwaj, 1997; Fugier-Vivier *et al.,* 1997; Grosjean *et al.,* 1997; Kaiserlian *et al.,* 1997; Schnorr *et al.,* 1997). However, little or no such evidence exists *in vivo*. DC express both CD46 and SLAM. With *in vitro* infection, two events are seen. Early on, cocultures of MV-infected DCs and T cells interfere with DC and T cell function associated with IL-12 production and CD40 signaling. Later, by day 3 to 4, DC integrity and viability become markedly compromised, with death by apoptosis approaching levels of 40 to 70%. Poor antigen presentation by DC, enhanced MV production (up to 18-fold, by activated T cells), and increased syncytial formation results in death of 90% of cells, presumably mediated by the TNF-rec superfamily.

Past assessment of the CNS during uncomplicated MV infection revealed lymphocyte infiltration into the cerebral spinal fluids and abnormal electroencephalograms (Gibbs *et al.,* 1959; Katz, 1995). Study of autopsy material from those dying of diseases other than viral infection have found MV antigens or nucleic acid sequences (Haase *et al.,* 1981; Katayama *et al.,* 1995) in the CNS. Further, chronic and persistent MV infection involves primarily the CNS (Griffin, 2001; Katz, 1985) with the neuron most often infected.

Hence, the understanding of MV tropism, spread, and pathogenesis requires the identification of a common receptor or alternatively several distinct receptors or coreceptor molecules involving cells of the nasal–respiratory tract, lymphoid cells, and CNS. Recent studies with other DNA or RNA viruses have most often pointed to usage of several receptors as opposed to a single universal receptor (reviewed in Baranowski *et al.,* 2001; Fields Virology, 2001).

In the accompanying minireview by Yanagi and colleagues (2002), evidence is presented primarily for in-

[1] To whom correspondence and reprint requests should be addressed. Fax: 858-784-9981. E-mail: mbaobo@scripps.edu.

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TABLE 1

Differential Expression of MV Receptor Molecules SLAM and CD46 on Target Cells

Cells	Expression of SLAM	Expression of CD46
B95-8 marmoset	++++ (100%)	nil (0%)
Neurons		
Line TMR-2	nil (0%)	++++ (100%)
Line CHR-16	nil (0%)	++++ (100%)
Fetal	nil (0%)	++++ (>80%)
Nasal epithelial cells[a]	± (0.5–3%)	++++ (>98%)
Lymphocyte	++++ (10–24%)[b]	
CD4 and CD8	++++ (100%)[c]	++++ (100%)[b]

[a] Nasal scrapes were obtained on 10 individuals by Dr. D. Stevenson (Scripps Clinic), separated in single-cell suspension with trypsin/EDTA, washed in buffer containing sera, and double-sorted using monoclonal antibody (mAb) to integrin labeled with Alexa 488 to identify epithelial cells and with mAbs to either SLAM or CD46 conjugated to Cy5 and then analyzed by FACS.

[b] Nonexperimentally activated PBL.

[c] Upon experimental activation.

volvement of SLAM with mention of CD46 and a non-SLAM non-CD46 receptor for MV. This appears, at this time, to be the most reasonable assessment of MV receptor usage. With a series of elegant studies, Yanagi first associated SLAM as a receptor for MV (Tatsuo *et al.,* 2000) and his minireview (Yanagi *et al.,* 2002) traces that work and its implications. Subsequent work by Hsu *et al.* (2001) confirmed Yanagi's observation and showed SLAM as a receptor for lymphotropic strains of MV. Our studies of SLAM or CD46-receptor expression on the clinical target cells of MV have failed, under conditions used, to detect SLAM on nasal–epithelial cells of human subjects or on cultured neurons, although CD46 molecules were detected with ease (Table 1). Interestingly, analysis of a variety of cell markers on the 1 to 3% of SLAM-positive cells in nasal scrapes showed no cosegregation of SLAM with $\alpha V\beta 5$, a marker for normal epithelia or dendritic cells; with CD14, a marker for macrophages; or with conventional markers for intraepithelial human T cells. This suggests that a previously unknown and to be defined cell in the nasal mucosa bears SLAM.

The weight of evidence currently on hand suggests that multiple (different) receptors are likely to be involved in MV spread and pathogenesis. Future investigation of acute MV infection and identification of the receptor on the cell infected by MV should be illuminating. Similarly and concurrently, the several laboratories making and utilizing human SLAM expressing transgenic mice alone and crossed to CD46 receptor bearing transgenic mice may well provide information on the use of these receptors in the spread of MV infection.

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